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# Docetaxel-based chemotherapy in the treatment of gastric cancer

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Docetaxel-based chemotherapy appears to have considerable promise in advanced gastric cancer. In phase II studies of single agent docetaxel, response rates (RRs) of 17% to 24% have been achieved in previously untreated patients. Importantly, RRs of 20% to 22% are seen in second-line treatment. Work by a Swiss and Italian collaborative group has shown that the combination of docetaxel 85 mg/m$^2$ with cisplatin 75 mg/m$^2$ every 3 weeks is quite active, achieving an RR of 55% and median survival of 9 months. Hematotoxicity was the main adverse event but was manageable. In other respects the docetaxel/cisplatin doublet (TC) was relatively well tolerated. The same group demonstrated that continuous infusion of 5-fluorouracil (5-FU) 300 mg/m$^2$ can be given on 2 weeks out of 3 to patients receiving TC. The addition of 5-FU, by this schedule, to TC (TCF) does not increase hematological toxicity, and does not compromise the tolerability of TC. An overall RR of 55% has been reported with TCF. A randomized phase II comparison of TC or TCF versus an ECF (epirubicin/cisplatin/5-FU) control arm is ongoing and should lead to a randomized phase III trial comparing TC or TCF with ECF. In an already completed international randomized phase II comparison of TC versus TCF (TAX-325), the three-drug combination proved significantly more active (RR 54% versus 32% with TC, among patients treated per protocol). Time to progression was also longer for TCF. Gastrointestinal (but not hematological) toxicity was less with TC. TCF was chosen for ongoing phase III comparison against a control 5-FU/cisplatin arm. It is possible that data from these randomized studies will confirm the value of docetaxel-based chemotherapy in advanced gastric cancer and that docetaxel combinations will also be effective in the multidisciplinary efforts to cure earlier stage cancer.

## Introduction

Gastric carcinoma remains a major health problem in many regions of the world. Incidence is extremely high in Oriental, South American and Eastern European countries, but is also significant in North America, Australia and Western Europe. Trends in incidence and other aspects of the epidemiology of gastric cancer are reviewed in detail elsewhere in this volume [1, 2].

Advanced gastric cancer remains incurable, and patients have a median survival of 6–9 months. While chemotherapy can prolong survival and improve quality of life when compared with best supportive care alone, no one agent or combination regimen has become accepted as the standard of treatment [1, 2]. Among the single agents with proven activity in the first-line setting are 5-fluorouracil (5-FU), cisplatin, etoposide, irinotecan, mitomycin, paclitaxel, S-1 and UFT (uracil/tegafur). With these agents, response rates (RRs) ranging from 14% to 44% have been reported. 5-FU, cisplatin, paclitaxel and irinotecan have also been used as single agents second line, achieving RRs of 12% to 26% [3–12].

Attempts to improve on these modest activities have taken a variety of forms. In Italy, there was an attempt to intensify treatment, using growth factor support, by adopting a weekly schedule. In the ECF (epirubicin/cisplatin/5-FU) regimen, 5-FU is given by protracted infusion, and this old drug has also been tried in novel high-dose guises. However, there is also considerable interest in the potential of relatively new cytotoxic agents, such as docetaxel. This promising taxane has now been extensively assessed in advanced gastric cancer. The data obtained with docetaxel as a single agent and in combination are the focus of this paper.

## Single-agent docetaxel

A series of phase II trials shows that docetaxel monotherapy has appreciable activity in gastric cancer. In the second-line setting, Vanhoefer et al. [13] achieved an RR of 20% in 25 evaluable patients administered docetaxel 100 mg/m$^2$. Also in second-line patients, Taguchi et al. [14] administered docetaxel 60 mg/m$^2$ and reported a 22% RR in 45 evaluable cases. In previously untreated patients, single-agent docetaxel has achieved RRs of 18%, 20% and 24% when given at 100 mg/m$^2$, and 18% when used at the slightly lower dose of 75 mg/m$^2$ [15–18]. The major single-agent toxicity is hematological [19].

## Docetaxel in combination with cisplatin: a European study

Prompted by these results, the Swiss Group for Clinical Cancer Research (SAKK) and the European Institute for Oncology (EIO) in Milan undertook to collaborate in studying the combination of

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docetaxel with cisplatin, which had already been extensively used in gastric cancer.

In an initial phase II trial ($n$ = 48), docetaxel 85 mg/m$^2$ over 1–2 h was given together with cisplatin 75 mg/m$^2$ over 4 h every 3 weeks for up to eight cycles. The RR by intention-to-treat was 52% in 48 patients, two of whom experienced a complete response [20]. The median time to progression (TTP) was 6.6 months, and the median overall survival time was 9 months. There were two deaths, one a suicide.

Grade 3 [NCI Common Toxicity Criteria (CTC)] leucocyte toxicity was seen in 40% of patients and grade 4 toxicity in 11%. Grade 3 granulocyte toxicity was observed in 24% of patients and grade 4 toxicity in 57%. This level of hematological toxicity was expected and manageable: none of the nine episodes of febrile neutropenia was fatal.

Other toxicities were relatively mild (Table 1). Grade 3 nausea and vomiting was experienced in 1% of cycles, grade 3 fatigue in 2%, grade 3 diarrhea in 2% and grade 3 mucositis in 2%. The incidence of grade 3 neuropathy was 0.4%. No grade 4 non-hematological toxicities were seen.

## The SAKK-EIO experience with docetaxel/cisplatin/5-FU

Having demonstrated the activity and tolerability of docetaxel/cisplatin (TC), consideration was given to further developing the doublet. When administered by continuous infusion, 5-FU is not hematotoxic. Moreover, it could play a significant part in the activity of the ECF regimen since, while 5-FU is given at 200 mg/m$^2$ per day, the doses used of epirubicin (50 mg/m$^2$) and cisplatin (60 mg/m$^2$) are modest. 5-FU therefore appeared to be a logical choice for adding to TC, forming the triplet TCF (docetaxel/cisplatin/5-FU).

In the dose escalation program used, the amount of cisplatin administered was increased from an initial 60 mg/m$^2$ (in dose levels I and II) to 75 mg/m$^2$ (at dose levels III–VIII), while that of docetaxel increased in stages from 70 mg/m$^2$ (at dose level I) to 85 mg/m$^2$ (at dose levels II to VIII), and that of 5-FU from 200 mg/m$^2$ (at dose levels I–III) to 225, 250, 275, 300 and 350 mg/m$^2$ (at dose levels IV, V,VI, VII and VIII, respectively) [21]. It proved possible to maintain the docetaxel 85 mg/m$^2$ and cisplatin 75 mg/m$^2$ doses used in TC while adding 300 mg/m$^2$ continuous infusion 5-FU on 2 weeks out of 3. The amount of hematoxicity observed was little different from that seen with TC: grade 3 (NCI-CTC) leucocyte toxicity was experienced by 44% and grade 4 toxicity by 8% of patients; grade 3/4 granulocyte toxicity occurred in 27%/54% of patients. Ten episodes of febrile neutropenia were seen in nine patients. Full results regarding the safety profile and the efficacy of the regimen are about to be submitted for publication.

**Table 1.** Non-hematological adverse events with the combination of docetaxel with cisplatin in 229 cycles [20, 21]

| | Grade (NCI-CTC)(%) | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Nausea/vomiting | 29 | 12 | 1 |
| Fatigue | 40 | 21 | 2 |
| Diarrhea | 5 | 5 | 2 |
| Mucositis | 13 | 4 | 2 |
| Neuropathy | 14 | 8 | 0.4 |
| Fluid retention | 9 | 4 | 0 |
| Anaphylactoid reaction | 2 | 0 | 0.4 |

## TAX-325: a multinational phase II/III trial of TC versus TCF

In parallel with the SAKK-EIO initiative, a multinational effort was mounted to conduct a randomized phase II comparison of TC versus TCF [22]. The purpose of the study was to identify the experimental arm to be taken forward into a phase III comparison against cisplatin/5-FU. The independent Data and Safety Monitoring Committee charged with making this decision had access to data on RR, TTP and safety as the trial progressed.

### Design and patient characteristics

In TAX-325, 158 patients with advanced gastric cancer (99% of them without prior chemotherapy) were randomized to receive either docetaxel 85 mg/m$^2$ plus cisplatin 75 mg/m$^2$ every 3 weeks (TC) or docetaxel 75 mg/m$^2$ plus cisplatin 75 mg/m$^2$ on day 1 plus continuous infusion 5-FU 750 mg/m$^2$ on days 1–5 every 3 weeks (TCF) (Figure 1) [22]. Data are presented both for patients who were treated per protocol, and for the entire intention-to-treat population.

Table 2 shows that patient and disease characteristics were reasonably well balanced across the two arms of the study. Those involved were predominantly male, relatively young and had a good performance status. All but 21% of patients had disease in more than one organ, and in the majority of cases the liver and/or peritoneum were involved. In a deliberate attempt to avoid the possibly confounding effects of surgical intervention, the aim was to avoid accruing patients with only localized disease. Hence, all but 2% of the entire study population had metastatic disease.

**Table 2.** TAX-325: characteristics of patients and disease treated with docetaxel/cisplatin (TC) or TC plus 5-FU (TCF) [22]

| | TC ($n$ = 76) | TCF ($n$ = 79) |
|---|---|---|
| Male (%) | 71 | 80 |
| Median age (years) | 55 | 54 |
| Median performance status (%) | 90 | 90 |
| No prior chemotherapy (%) | 99 | 99 |
| No. of organs involved (%) | | |
| 2 | 41 | 39 |
| ≥3 | 37 | 41 |
| Metastatic disease (%) | 100 | 98 |
| Metastatic disease involving liver and/or peritoneum (%) | 71 | 63 |
| Bidimensionally measurable disease (%) | 72 | 86 |

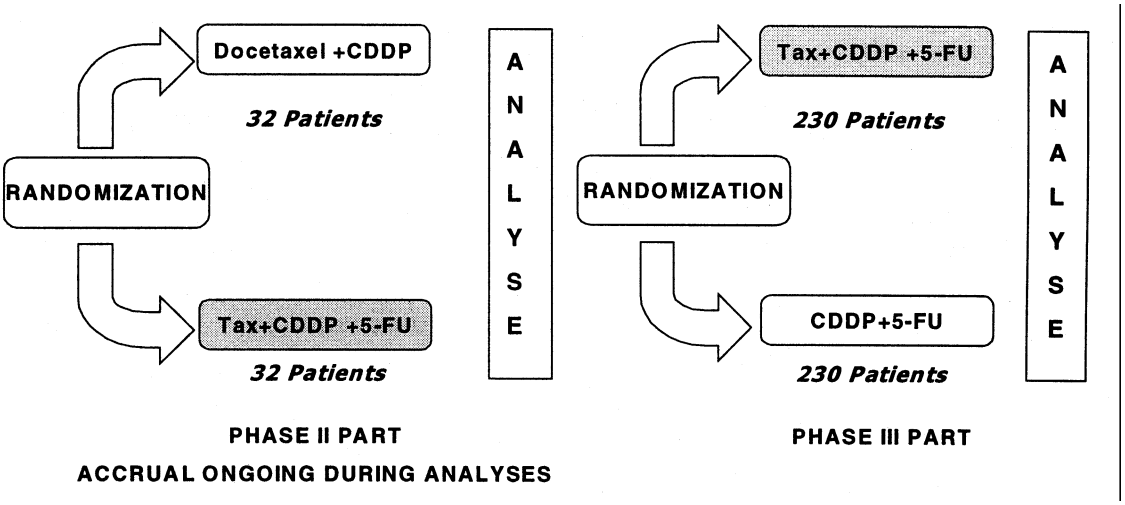


**Figure 1.** TAX-325 phase II–III study design.

The relative dose intensity across the study was uniformly high: 0.98 for docetaxel and 0.96 for cisplatin in the TC arm; and 0.93 for docetaxel, 0.92 for cisplatin and 0.92 for 5-FU in the TCF arm. The doses stipulated for the trial therefore proved in practice to be appropriate across the range of participating institutions.

### Efficacy

Considering only those patients treated per protocol, the RR in the TC arm was 32% (among 63 patients) and that in the TCF arm 54% (among 61 patients). By intention-to-treat analysis of the full population, the RRs were 28% (in 76 patients) and 43% (in 79 patients), respectively. The difference between the two arms is therefore maintained.

TCF was also superior in TTP, which was 5 months in the TC arm and 5.9 months with TCF (intention-to-treat analysis). The figures for overall survival showed a median of 10.5 months with TC versus 9.6 months with TCF. It should be noted that this phase II study was not powered to detect differences in overall survival time as the end point. The objective of this phase II study was to select the best combination for a phase III trial based on response rate.

### Toxicity

Toxicity, particularly of the gastrointestinal tract, was greater with the TCF combination than with TC. Grade 3/4 (NCI-CTC) stomatitis was seen in 9.6% of TCF cycles but in no TC cycle. The corresponding figures for diarrhea were 4.6% and 1.2%, and for nausea 4.8% and 3.2%. Where grade 3/4 stomatitis and diarrhea occurred, the problem was usually evident in the first or second cycle, and could be resolved by dose reduction.

Hematological toxicities were similar across the two arms of the trial. Grade 3/4 neutropenia was seen in 62% of TC cycles and 52% of TCF cycles. However, the incidence of febrile neutropenia was low (3% of TC cycles; 5% of TCF cycles), and there was one treatment-related death in the TCF arm.

Based on the evidence of greater RR and longer TTP, and despite greater gastrointestinal toxicity, the independent Data Monitoring Committee elected the TCF regimen as the experimental arm of the phase III portion of the trial. More than 300 patients have now been accrued, with a planned interim analysis scheduled for summer 2002.

## Discussion

The data reviewed above are derived from phase II studies (one of which randomized patients to TC or TCF). They must therefore be considered preliminary. However, there are two grounds for hoping that the development of TC/TCF represents an advance. First, there is consistency between the trials. Table 3 shows the five published phase II studies that have investigated TC and TCF regimens. Overall, the RRs range from 33% to 56%. TTPs, where reported, range from 5 to 6.6 months, and median overall survival time from 9 to 10.5 months. There is an impressive homogeneity in these results [20–24].

Secondly, data from second-line studies show that docetaxel can induce a response in patients who have already failed other agents. Vanhoefer et al. [13] report a 20% RR in 25 patients already exposed to first-line 5-FU and cisplatin (FUP). André et

**Table 3.** Efficacy data from the five phase II studies of docetaxel/cisplatin (TC) and docetaxel/cisplatin/5-FU (TCF) in advanced gastric cancer [20–24]

| Regimen [ref.] | No. of patients | RR (%) | TTP (months) | Overall survival (months) |
|---|---|---|---|---|
| TC [20, 21] | 48 | 56 | 6.6 | 9.0 |
| TC [22] | 63 | 35 | 5.0 | 9.6 |
| TCF [22] | 61 | 56 | 5.9 | 10.5 |
| TC [23] | 43 | 37 | 6.1 | 10.4 |
| TC [24] | 46 | 33 | – | 9.0 |

RR, response rate; TTP, time to progression.

al. [25] found a 21% RR when 25 patients pre-treated with FUP were given epirubicin 75 mg/m$^2$ plus docetaxel 75 mg/m$^2$ every 3 weeks; and Giuliani et al. [26] reported a 17% RR with second-line single-agent docetaxel 100 mg/m$^2$. These data suggest that using several agents up-front in a docetaxel-based combination should have a substantial effect in chemotherapy-naive patients.

Nevertheless, data from randomized trials are required. To this end, the SAKK-EIO group is collaborating with centers in the UK on a phase II study in which patients are randomized to TC or TCF or ECF. Whichever performs better out of the TC and TCF arms will then move into a phase III comparison with ECF. This trial will complement the ongoing international phase III comparison of TCF against FUP.

A randomized trial of neoadjuvant TCF has also begun in the hope that docetaxel-based combinations will be able to contribute in the multidisciplinary effort to cure earlier stage disease.

## Disclosure

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